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Maternal Obesity, Uterine Activity, and the Risk of Spontaneous Preterm Birth

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Abstract

OBJECTIVE—To assess the associations between maternal obesity, uterine contraction frequency, and spontaneous preterm birth in at-risk women.

METHODS—In a secondary analysis, we analyzed data from 253 at-risk women (prior spontaneous preterm birth, vaginal bleeding) enrolled in a multi-center observational study of home uterine activity monitoring at 11 centers. All women wore a uterine activity monitor twice daily from 22 through 34 weeks of gestation. Mean and maximal contractions/hour at 22-24, 25-26, 27-28, 29-30, 31-32, and at or after 33 weeks of gestation were compared between overweight/obese women (a BMI at 22-24 weeks greater than 25 kg/m²) and normal/underweight women (a BMI of at least 25 kg/m²) at each gestational age interval. Multivariable analysis evaluated the influences of BMI,

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contractions, fetal fibronectin and transvaginal cervical length on spontaneous preterm birth before 35 weeks.

RESULTS—Obese/overweight women (n=156) were significantly less likely to experience spontaneous preterm birth before 35 weeks (8.3 vs 21.7%, $p<0.01$). For each gestational age interval before 32 weeks, obese/overweight women had fewer mean contractions/hour ($P<0.01$ for each) and maximal contractions/hour ($p<0.01$ for each) than normal/underweight women, although their mean cervical lengths (34.3 vs 33.1 mm, $p=0.25$), and fetal fibronectin levels (7.1% vs. 7.2% ≥ 50 ng/mL, $p=0.97$) were similar at study enrollment. Obese/overweight status was associated with a lower risk of spontaneous preterm birth before 35 weeks after controlling for contraction frequency and other factors evaluated at 22-24 and 31-32 weeks, but not at later time periods.

CONCLUSION—Obese/overweight women at risk for spontaneous preterm birth exhibit less uterine activity and less frequent spontaneous preterm birth before 35 weeks of gestation than normal/underweight women.

The prevalence of obesity in the United States continues to rise, with 33.1% and 33.2% of adult men and women classified as obese (body mass index [BMI] ≥ 30 kg/m²) in 2003-2004¹. The obstetric population is similarly affected, with 22.4% of women delivering in 2001-2004 conceiving while obese with another 23% being overweight².

Pregravid body habitus is related to the risk of peripartum complications including hypertension and preeclampsia, diabetes, macrosomia and labor arrest, as well as cesarean delivery and post-operative complications such as wound disruption and venous thromboembolism³. Preconceptional body habitus also may influence the timing of parturition. Low pregravid BMI and inadequate weight gain are independent risk factors for preterm birth^{4, 5}. Change in BMI between pregnancies may alter the risk of recurrent preterm birth⁶, in that weight loss after a preterm delivery may increase the risk of recurrence. Conversely, the risk of spontaneous preterm birth (SPB) decreases with increasing maternal BMI^{7, 8}. The mechanisms responsible for reduced SPB among obese/overweight women are not known. One plausible explanation is a reduction in uterine activity in these women.

The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (NICHD-MFMU) Home Uterine Activity Monitoring Study (HUAM) was a prospective study that evaluated the association between uterine activity and SPB.^{9, 10}. We postulated that, in spite of issues thought to exist in the accuracy of monitoring in this population, overweight/obese women would demonstrate less frequent uterine activity remote from delivery than non-overweight/obese women, and that this decreased activity would be associated with a lower risk of SPB. The purpose of this study is to assess the associations between maternal obesity, uterine contraction frequency and spontaneous preterm birth (SPB) in at-risk women

Materials and Methods

This is a secondary analysis of data collected in a prospective observational cohort study conducted by the NICHD-MFMU Network. The primary study was conducted at 11 centers between 1994 and 1996. The original study design and population have been previously described⁹. Approval from the human-subjects review board was received at each institution. All women provided written informed consent. Briefly, women with singleton pregnancies at increased risk for preterm birth (history of one or more spontaneous preterm deliveries between 20 and 36 weeks of gestation, or second-trimester vaginal bleeding in the current pregnancy) were recruited. Women receiving or planning to use HUAM, prophylactic tocolytic therapy, or with a cervical cerclage in place were ineligible, as were those diagnosed with placenta previa or major fetal anomaly.

Screening for eligibility took place prior to 22 weeks of gestation as confirmed by ultrasound. Enrolled subjects underwent twice daily HUAM from 22-34 weeks and were seen for study visits scheduled at 22-24 (visit 1), 25-26 (visit 2), 27-28 (visit 3), 29-30 (visit 4), 31-32 (visit 5), and 33 or more (visit 6) weeks. Women were instructed by trained research nurses to monitor for contractions using a uterine activity monitor for a period of one hour at least twice daily in sessions at least two hours apart. The first session was to be between 4 AM and 3:59 PM, and the other between 4 PM and 3:59 AM. Monitoring was performed on 2 or more days per week from enrollment to 28 weeks' and on 4 or more days per week after 28 weeks'. Subjects were considered compliant if they held to the schedule of home monitoring and returned for visits 3 and 5. Cervicovaginal fluid swabs for fetal fibronectin (fFN) testing were obtained at each study visit, and quantitatively assayed according to previously published protocols.¹¹ Transvaginal ultrasound cervical length measurements, obtained as previously described¹² and digital examinations were performed at visits 1, 3 and 5.

For this analysis, data were analyzed from subjects grouped according to BMI at 22-24 weeks as "obese/overweight" ($\text{BMI} > 25 \text{ kg/m}^2$) or "normal/underweight" ($\text{BMI} \leq 25 \text{ kg/m}^2$). For each specified time period, the mean number of contractions per hour and maximal number of contractions per hour were calculated for each patient, and compared between the two groups.

Statistical analysis was conducted using SAS software, version 8.2 (SAS Institute, Cary, NC). Continuous variables were compared using the Wilcoxon rank sum test. Categorical variables were analyzed using Chi-square, Fisher's exact, or Mantel Haenszel chi-square trend¹³ test, where appropriate. Multivariable analysis included logistic regression to evaluate the independent association between maternal body habitus (as a discrete variable: obese/overweight versus normal/underweight, and as a continuous variable: increasing BMI) and contraction frequency on spontaneous preterm delivery, both with and without adjustment for fFN and cervical length measures. This modeling was restricted to three time periods (22-24, 27-28, and 31-32 weeks), when both fFN and cervical length were collected. A two-tailed nominal p-value < 0.05 was considered significant. No adjustments were made for multiple comparisons.

Results

Two-hundred fifty-three compliant subjects with singleton pregnancies and BMI data available were included in this analysis (obese/overweight=156; normal/underweight=97). Indications for inclusion were a history of one prior spontaneous preterm birth, ($N=194$, 76.7%), two or more prior preterm births ($N=56$, 22.1%), and second trimester vaginal bleeding ($N=8$, 3.2%). Five women had both vaginal had bleeding and at least one prior preterm birth. At enrollment, baseline characteristics including maternal race, parity, tobacco use, height, Bishops score, sonographic cervical length, and fetal fibronectin levels were similar between groups (Table 1). When compared with normal/underweight women, obese/overweight women were older ($27.3 \text{ v } 24.6 \text{ yrs}$, $p < 0.01$). The use of tocolytic drugs was evenly distributed between groups, with 24 (24.7%) subjects exposed in the low/normal weight group and 31 (19.9%) in the overweight/obese group ($p=0.36$).

Spontaneous preterm birth before 35 weeks occurred in only 8.3% ($n=13$) of overweight and obese women, as opposed to 21.7% ($n=21$) of normal and underweight ($p < 0.01$). In this same cohort, indicated preterm birth rates were not different between groups [5/156 (3.2%) of the overweight/obese and 4/97 (4.1%) of the normal/underweight ($p=0.74$)]. For each gestational age interval before 32 weeks, obese/overweight women had fewer mean contractions/hour ($P < 0.01$ for each; Table 2) and maximal contractions/hour ($p < 0.01$ for each; Table 2) than normal/underweight women. Table 3 describes the results for multivariable analysis including various clinical characteristics. When mean contraction frequency and overweight/obese were

simultaneously used to predict SPB <35 weeks, overweight/obese was always associated with decreased risk of early delivery ($p < 0.02$ for each time period), but there was no association between contraction frequency and early delivery after adjusting for obese/overweight status ($p > 0.05$ in all cases). When BMI was analyzed as a continuous variable, a significant interaction between BMI and contraction frequency was found in relationship to SPB <35 weeks ($p < 0.05$). In the presence of increasing BMI, the relationship between contraction frequency and risk for SPTB strengthens. This interaction was significant at 22-24 weeks and 31-32 weeks, but not at 27-28 weeks.

Distinct multivariable analyses were performed that included cervical length and fetal fibronectin. These analyses revealed fetal fibronectin to be associated with an increased risk and maternal obese/overweight status with a decreased risk of SPB before 35 weeks at 22-24 weeks ($p = 0.02$ for both), but not at 27-28 or 31-32 weeks. Increased mean and maximum contractions were associated with an increased risk at 27-28 weeks only ($p = 0.01$), while increased cervical length at all three time periods was associated with a lower risk of SPB ($P < 0.01$ for each). Findings were similar when BMI was analyzed as a continuous variable. However, the interactions between BMI and contraction frequency observed in the unadjusted model did not remain significant after adjustments for fetal fibronectin and cervical length.

Discussion

We have found obese and overweight women who are at risk for preterm birth to have less frequent uterine contractions and lower maximal contraction frequency between 22 and 34 weeks' gestation, as detected by external tocometry. Increasing BMI and decreasing contraction frequency remote from delivery were independently associated with a lower risk of spontaneous preterm birth, after controlling for other factors at some gestational ages, but not others. In this high-risk cohort, we have confirmed prior data showing that heavier women are at a lower risk for spontaneous preterm birth before 35 weeks⁷. After controlling for other factors, our analysis did not find significant relationships between contraction frequency and SPB at 22-24 or 31-32 weeks, but did at 27-28 weeks.

Published literature regarding a possible protective effect of obesity on preterm delivery risk is inconsistent in both study groups and outcome. Our work concurs with previous studies by Hendler⁷ and Smith¹⁴ showing a reduction in the rate of spontaneous preterm delivery among obese parturients. Hendler et al showed obese women to have significantly fewer preterm births < 37 weeks (6.2% vs 11.2%; $P < 0.001$) and <34 weeks (1.5% vs 3.5%; $P = 0.012$). Smith et al showed that as BMI increased, the risk of indicated preterm birth increased, while that of spontaneous preterm birth decreased ($P < 0.001$). Others have observed an increased risk of preterm birth amongst obese gravidas. In a large retrospective study evaluating the role of body habitus in prematurity among nulliparous women¹⁵, obesity was associated with an increased risk of preterm birth <32 weeks when compared to lean control subjects ($BMI < 20 \text{ kg/m}^2$) after adjustment for other factors (OR 1.6; 95% CI 1.1, 1.3). Study of the same cohort by Cedergren found increased risk of preterm birth at <37 and <32 weeks (5.4% vs 4.5% and 0.8% vs 0.6%, respectively). These studies did not distinguish clearly between indicated and spontaneous deliveries, and were retrospective in nature. The differences in these studies may be due in part to differences in study populations, definitions of weight categories, and evaluated outcomes.

Potential explanations for our findings include an endocrine effect of increased adipose tissue on uterine contraction frequency or a technical measurement artifact related to difficulty in monitoring uterine contractions when the maternal abdomen is obese. The latter explanation is plausible, but if true would be expected to decrease in significance with gestational age as the uterine fundus is more easily identified in women with normal or low BMI. Furthermore,

after controlling for other confounding variables, the risk of spontaneous preterm birth was decreased in the obese and overweight group independent of uterine activity when screened at 22-24 weeks' gestation. As a consequence, when screening for risk of preterm delivery, overweight and obese women who demonstrate similar contraction frequency patterns to normal and underweight women may therefore be at particular risk to deliver prior to term.

The relationship between obesity and a reduced risk of spontaneous preterm birth is unexplained. Obesity is known to be a pro-inflammatory state in which the serum levels of inflammatory modulators associated with preterm birth, e.g., TNF- α , IL-6, and IL-8, are elevated. On the other hand, obesity is associated with lower rates of cervical length < 25mm. Abnormal body habitus may affect timing of parturition through changes in cervical length.

Maternal obesity appears to be associated with less frequent SPB through an unknown mechanism other than uterine quiescence. While lack of cervical shortening may play a role, further study will be needed to describe the influence of body habitus on parturition, and to perhaps take advantage of whatever process is at work in future efforts to prevent spontaneous preterm birth.

PRECIS

In high-risk women, overweight/obese body habitus is associated with significantly fewer uterine contractions throughout pregnancy, and a lower risk of spontaneous preterm birth.

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Table 1

Clinical characteristics, cervical length and fetal fibronectin results at study enrollment at 22-24 weeks

	BMI ≤ 25 kg/m²	BMI > 25 kg/m²	p-value
	N = 97	N = 156	
Maternal age (years)	24.6 ± 4.9	27.3 ± 5.9	<0.01
Parity	1.7 ± 0.8	2.1 ± 1.4	0.22
Race			
African American	55 (56.7)	95 (60.9)	0.57
Caucasian	39 (40.2)	53 (34.0)	
Other	3 (3.1)	8 (5.1)	
Smoked during this pregnancy	34 (35.1)	39 (25.0)	0.09
Height (in)	64.2 ± 3.2	64.0 ± 2.8	0.74
Weight (kg)	58.5 ± 7.6	83.9 ± 16.6	<0.01
Body mass index (kg/m ²)	22.0 ± 2.0	31.8 ± 6.2	<0.01
Fetal fibronectin ≥50 ng/mL	7 (7.2)	11 (7.1)	0.97
Transvaginal cervical length (mm)	33.1 ± 9.3	34.3 ± 8.5	0.25
Bishop score			
0	17 (17.5)	16 (10.3)	0.81
1	24 (24.7)	49 (31.4)	
2	23 (23.7)	38 (24.4)	
3	17 (17.5)	34 (21.8)	
4	10 (10.3)	13 (8.3)	
5	6 (6.2)	5 (3.2)	
6	0	1 (0.6)	

Data are presented as mean ± standard deviation or n (%)

Table 2

Mean and maximum contraction rate as monitored by HUA/M at each observation period in overweight/obese and normal/underweight women

Weeks of gestation	Mean contraction rate per hour		p-value	Maximum contraction rate per hour		p-value
	BMI ≤ 25 kg/m ² (N = 97)	BMI > 25 kg/m ² (N = 156)		BMI ≤ 25 kg/m ² (N = 97)	BMI > 25 kg/m ² (N = 156)	
24	0.13 (0.0 - 0.44)	0.0 (0.0 - 0.14)	<0.001	1.00 (0.0 - 2.00)	0.0 (0.0 - 1.00)	<0.001
25-26	0.17 (0.06 - 0.49)	0.0 (0.0 - 0.15)	<0.001	1.00 (1.00 - 3.00)	0.0 (0.0 - 1.00)	<0.001
27-28	0.29 (0.07 - 0.63)	0.05 (0.0 - 0.24)	<0.001	2.00 (1.00 - 4.00)	1.00 (0.0 - 2.00)	<0.001
29-30	0.31 (0.11 - 0.81)	0.10 (0.0 - 0.35)	<0.001	2.00 (1.00 - 4.00)	1.00 (0.0 - 2.86)	<0.001
31-32	0.32 (0.13 - 0.89)	0.19 (0.04 - 0.49)	<0.001	2.00 (1.00 - 4.03)	1.09 (1.00 - 3.00)	0.007
33 or greater	0.49 (0.19 - 1.06)	0.25 (0.07 - 0.67)	0.002	3.00 (2.00 - 5.17)	3.00 (1.00 - 5.00)	0.09

Data are presented as median (interquartile range)

Table 3

Comparison of HUAM contraction rates observed in overweight/obese and normal/underweight women

Week of Gestation	BMI <25 kg/m ²			BMI >25 kg/m ²			Adjusted OR (95% CI) *
	N	Fetal fibronectin >50 ng/mL	Transvaginal SPB <35 weeks	N	Fetal fibronectin >50 ng/mL	Transvaginal SPB <35 weeks	
22-24	93	7 (7.2%)	33.1 ± 9.3 (22.6%)	151	11 (7.1%)	34.3 ± 8.5 (8.6%)	13 (0.36)
27-28	95	5 (5.7%)	28.8 ± 8.6 (21.1%)	154	12 (8.0%)	32.2 ± 9.0 (7.8%)	12 (0.49)
31-32	88	8 (11.1%)	26.4 ± 9.8 (15.9%)	147	13 (10.8%)	30.0 ± 8.4 (5.4%)	8 (0.37)

Data are presented as mean ± standard deviation or n (%)

SPB = spontaneous preterm birth

* Odds and 95% confidence intervals of spontaneous preterm birth <35 weeks for BMI >25 kg/m² versus ≤25 kg/m², adjusted for fetal fibronectin and cervical length.